

-continued

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22

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&lt;220&gt; FEATURE:

&lt;223&gt; OTHER INFORMATION: Synthetic Construct

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19

What is claimed is:

1. A method for reducing lactate production in cultured cells, the method comprising culturing cells comprising a first heterologous nucleic acid sequence encoding a small interfering RNA (siRNA) specific for a lactate dehydrogenase (LDH) and a second heterologous nucleic acid sequence encoding an siRNA specific for a pyruvate dehydrogenase kinase (PDHK), wherein the first heterologous nucleic acid sequence is operably linked to a first promoter, and wherein the second heterologous nucleic acid sequence is operably linked to a second promoter, wherein the cultured cells have a polypeptide productivity of at least about 68% higher than cultured cells without the heterologous nucleic acid sequence comprising siRNA specific for PDHK and the siRNA specific for LDH.

2. The method of claim 1, wherein the LDH is LDHa.

3. The method of claim 1, wherein the cultured cells further comprise a third heterologous nucleic acid sequence encoding an siRNA specific for a second PDHK and wherein the third heterologous nucleic acid sequence is operably linked to a third promoter.

4. The method of claim 3, wherein the cultured cells further comprise a fourth heterologous nucleic acid sequence encoding an siRNA specific for a third PDHK and wherein the fourth heterologous nucleic acid sequence is operably linked to a fourth promoter.

5. The method of claim 4, wherein cultured cells further comprise a fifth heterologous nucleic acid sequence encoding an siRNA specific for a fourth PDHK and wherein the fifth heterologous nucleic acid sequence is operably linked to a fifth promoter.

6. The method of any one of claims 1, 3, 4, and 5, wherein the PDHK is selected from the group consisting of PDHK1, PDHK2, PDHK3, and PDHK4.

7. The method of claim 1, wherein the cultured cells produce a heterologous polypeptide.

8. The method of claim 7, wherein the heterologous polypeptide is an antibody.

9. The method of claim 4, wherein an average lactate production rate of the cultured cells is less than about negative 0.02 mg/10<sup>6</sup> cells/day.

10. The method of claim 4, wherein the cultured cells have a Specific Productivity of at least about 75% higher than cultured cells without the heterologous nucleic acid sequence comprising the siRNA specific for PDHKs and the siRNA specific for LDH.

11. The method of claim 4, wherein the cultured cells maintain an osmolality at less than about 300 mOsm over 14 days.

12. The method of claim 7, wherein the cultured cells are mammalian cells.

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